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NOTICE OF ALLOWANCE AND FEE(S) DUE

27683 7590 12/18/2009

HAYNES AND BOONE, LLP
IP Section
2323 Victory Avenue
Suite 700
Dallas, TX 75219

EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 12/18/2009

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,840	07/06/2001	Mark Leslie Smythe	36677.8	8048

TITLE OF INVENTION: AUXILIARY FOR AMIDE BOND FORMATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$0	$0	$755	03/18/2010

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

27683 7590 12/18/2009

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Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,840	07/06/2001	Mark Leslie Smythe	36677.8	8048

TITLE OF INVENTION: AUXILIARY FOR AMIDE BOND FORMATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$0	$0	$755	03/18/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
KAM, CHIH MIN	1656	514-002000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1656	

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Determination of Patent Term Extension under 35 U.S.C. 154 (b)
(application filed after June 7, 1995 but prior to May 29, 2000)

The Patent Term Extension is 0 day(s). Any patent to issue from the above-identified application will include an indication of the 0 day extension on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Extension is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability	Application No.	Applicant(s)	
	09/787,840	SMYTHE ET AL.	
	Examiner	Art Unit	
	CHIH-MIN KAM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *9/10/2009*.

2. ☒ The allowed claim(s) is/are *1-5,8-14,16-31,35 and 39-42*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

DETAILED ACTION

Status of the Claims

1. Claims 1-5, 7-14, 16-31, 35 and 39-42 are pending.

Applicant's amendment filed September 10, 2009 is acknowledged, and applicants' response has been fully considered. Claims 1-3, 14, 16, 22, 23, 35 and 40 have been amended, and claim 15 has been cancelled. Therefore, claims 1-5, 7-14, 16-31, 35 and 39-42 are examined.

Withdrawn Claim Objections

2. The previous objection to claims 2, 4, 5, 9-13, 15, 16, 23, 35 and 40 is withdrawn in view of applicants' amendment of the claims, applicants' cancellation of the claim, and applicant's response at page 28-29 in the amendment filed September 10, 2009.

Withdrawn Claim Rejections - 35 USC § 102

3. The previous rejection of claims 1, 3, 7, 8, 14 and 22, under 35 U.S.C. 102(b) as being anticipated by Johnson *et al.* (J. Peptide Sci. 1, 11-25 (1995)), is withdrawn in view of applicants' amendment of the claims, and applicants' response at pages 27-28 in the amendment filed September 10, 2009.

Examiner's Amendment

An **Examiner's Amendment** to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mark More on December 15, 2009.

Examiner's Amendment to the Claims:

Cancel claim 7.

Claims 1, 3, 4, 8, 9, 14, 16, 21-23, 35 and 40 have been amended as follows:

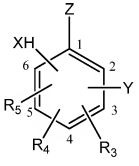
1. (Currently amended) A method of

a) synthesis of a linear or cyclic peptide;

b) synthesis of a C-terminal modified peptide; or

c) on-resin cyclization of a peptide molecule,

said method comprising at least the step of linking a cyclic aromatic auxiliary compound of General Formula II to a primary amine nitrogen atom of an amino acid, or of a peptide which is to be cyclized or modified, to form a secondary amine,



II

in which

XH is OH, SH, CH_2OH, or CH_2SH at position 2 or 3;

Y is an electron-withdrawing group at position 5 or 6;

Z is any group which allows the formation of a covalent carbon-nitrogen bond; and

R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy, alkoxy, aryloxy and a covalent linkage to a solid support; and

in which R^3 and R^4, or R^4 and R^5 can optionally together with the ring form a 5-, 6-, or 7-membered ring, thereby to facilitate conversion of the secondary amine to an amide, activating the carboxylic acid group of the amino acid, or of a peptide which is to be cyclized or modified, and converting the secondary amine to an amide.

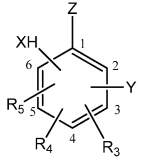
3. (Currently amended) A method of

a) synthesis of a linear or cyclic peptide;

b) synthesis of a C-terminal modified peptide; or

c) on-resin cyclization of a peptide molecule,

said method comprising at least the step of linking a cyclic aromatic auxiliary compound of General Formula II to a primary amine nitrogen atom of an amino acid, or of a peptide which is to be cyclized or modified, to form a secondary amine,



II

in which

XH is OH, SH, CH_2OH, or CH_2SH;

Y is an electron-withdrawing group;

Z is any group which allows the formation of a covalent carbon-nitrogen bond; and R^3, R^4 and R^5 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl aryloxy, XH or Y, or a covalent linkage to a solid support; and

in which R^3 and R^4, or R^4 and R^5 can optionally together with the ring form a 5-, 6-, or 7-membered ring, thereby to facilitate conversion of the secondary amine to an amide, activating the carboxylic acid group of the amino acid, or of a peptide which is to be cyclized or modified, and converting the secondary amine to an amide,

wherein Z is an ~~aldehyde,~~ alkylalcohol, alkylhalide, or a ketone, or is a halogenated C_{1-3} alkyl group.

4. (Currently Amended) The method of claim 3, in which the halogenated C_{1-3} alkyl group is a halogenated methyl group.

8. (Currently Amended) The method of claim ~~7~~1, in which the XH group is at position 2.

9. (Currently Amended) The method of claim ~~7~~1, in which Y is at position 6.

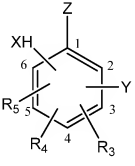
14. (Currently amended) A method of

a) synthesis of compound selected from the group consisting of linear and cyclic peptides, large peptides with a native backbone, and "difficult" peptide sequences,

b) backbone linkage for the synthesis of peptides, C-terminal modified peptide, or

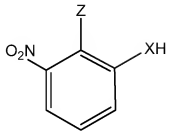
c) on-resin cyclization of a peptide molecule,

said method comprising at least the steps of: linking a cyclic aromatic auxiliary compound of General Formula II,



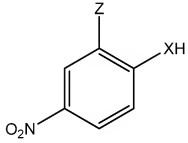
II

General Formula III,



III

or General Formula IV



IV

in which

XH is OH, SH, CH_2OH, or CH_2SH;

Y is an electron-withdrawing group;

Z is any group which allows the formation of a covalent carbon-nitrogen bond; and

R^3, R^4 and R^5 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, alkoxy, aryloxy, XH or Y, or a covalent linkage to a solid support, and

in which R^3 and R^4, or R^4 and R^5 can optionally together with the ring form a 5-, 6-, or 7-membered ring,

to a primary amine nitrogen atom of a starting peptide molecule, to form a secondary amine, thereby to facilitate conversion of the secondary amine to an amide, activating the C-terminal carboxylic acid group of the peptide, and converting the secondary amine to an amide;

wherein XH in General Formula II is at position 2, and Y is NO_2 at position 6.

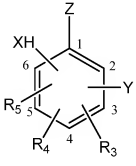
16. (Currently Amended) A method of

a) synthesis of a linear or cyclic peptide;

b) synthesis of a C-terminal modified peptide; or

c) on-resin cyclization of a peptide molecule,

said method comprising at least the step of linking a cyclic aromatic auxiliary compound of General Formula II to a primary amine nitrogen atom of an amino acid, or of a peptide which is to be cyclized or modified, to form a secondary amine,



II

in which

XH is ~~OH,~~ SH, CH_2OH, or CH_2SH;

Y is an electron-withdrawing group;

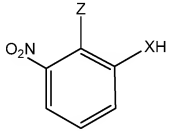
Z is any group which allows the formation of a covalent carbon-nitrogen bond; and

R^3, R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl, aryl, hydroxy, alkoxy, aryloxy and a covalent linkage to a solid support; and

in which R^3 and R^4, or R^4 and R^5 can optionally together with the ring form a 5-, 6-, or 7-membered ring, thereby to facilitate conversion of the secondary amine to an amide,

activating the carboxylic acid group of the amino acid, or of a peptide which is to be cyclized or modified, and converting the secondary amine to an amide.

21. (Currently Amended) The method of claim ~~17~~23, in which ~~activation of the C-terminal carboxylic acid is performed in the presence of an~~ the auxiliary compound is of General Formula III,



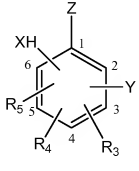
III

and the ~~cyclization is performed by attaching the auxiliary compound to the selected amine via the Z group~~ method further comprising removing the auxiliary compound by photolysis.

22. (Currently Amended) A method of synthesis of a large peptide with a native peptide backbone, comprising the steps of:

a) synthesizing a set of peptide fragments to be linked to form a large peptide;

b) linking a cyclic aromatic auxiliary compound of General Formula II



II

in which

XH is SH, CH_2OH, or CH_2SH;

Y is an electron-withdrawing group selected from the group consisting of nitro, ketone, carboxylic ester, amide, nitrile, sulfonamide, sulfoxide, sulfone, sulfonate, fluoride, chloride, bromide and iodide;

Z is selected from the group consisting of an alkylalcohol, an alkylhalide, a ketone, and a halogenated C_{1-3} alkyl group, and allows the formation of a covalent carbon-nitrogen bond; and

R^3, R^4 and R^5 are each independently substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, aryloxy, XH or Y, or a covalent linkage to a solid support; and

in which R^3 and R^4, or R^4 and R^5 can optionally together with the ring form a 5-, 6-, or 7-membered ring,

to the primary amine of the first peptide fragment to form a secondary amine, thereby facilitating conversion of the amine to an amide;

c) activating the C-terminal carboxylic acid of the second peptide fragment;

d) adding the second peptide fragment to the first peptide fragment and forming a peptide bond between the two fragments; and optionally

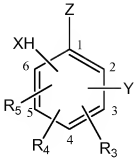
e) removing the auxiliary compound after N-acylation is complete,

wherein steps b) to e) are repeated to add the remaining members of the set of peptide fragments until the large peptide is completed.

23. (Currently Amended) A method of synthesis of a cyclic peptide, comprising the steps of

a) synthesizing a linear peptide to be cyclized,

b) ~~linking~~ activating a C-terminal carboxylic acid of the linear peptide in the presence of a cyclic aromatic auxiliary compound of General Formula II



II

in which

XH is OH, SH, CH_2OH, or CH_2SH;

Y is an electron-withdrawing group;

Z is any group which allows the formation of a covalent carbon-nitrogen bond; and R^3, R^4 and R^5 are each independently hydrogen, alkyl, substituted alky1, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl,[[-]]aryloxy, XH or Y, or a covalent linkage to a solid support; and

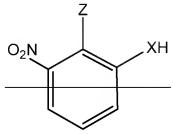
in which R^3 and R^4, or R^4 and R^5 can optionally together with the ring form a 5-, 6-, or 7-membered ring,

c) linking the auxiliary compound to a selected primary amine of the linear peptide to form a secondary amine, thereby facilitating conversion of the amine to an amide,

~~c)~~d) ~~activating a selected carboxylic acid to effect~~ performing cyclization, and where necessary inducing ring contraction, and optionally

~~d)~~e) removing the auxiliary compound after complete N-acylation~~;~~

~~wherein activation of the C-terminal carboxylic acid is performed in the presence of an auxiliary compound of General Formula III,~~



III

~~and the cyclization is performed by attaching the auxiliary compound to the selected amine *via* the Z-group;~~

~~and further wherein the auxiliary compound is removed by photolysis~~.

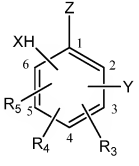
35. (Currently amended) A method of

a) synthesis of compound selected from the group consisting of linear and cyclic peptides, large peptides with a native backbone, and "difficult" peptide sequences,

b) backbone linkage for the synthesis of peptides, C-terminal modified peptide, or

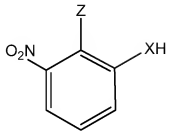
c) on-resin cyclization <u>of a peptide molecule</u>,

said method comprising at least the steps of: linking a cyclic aromatic auxiliary compound of General Formula II,



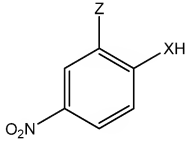
II

General Formula III,



III

or General Formula IV



IV

in which

XH is OH, SH, CH_2OH, or CH_2SH;

Y is an electron-withdrawing group;

Z is any group which allows the formation of a covalent carbon-nitrogen bond; and

R^3, R^4 and R^5 are each independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, alkoxy, aryloxy, XH or Y, or a covalent linkage to a solid support, and

in which R^3 and R^4, or R^4 and R^5 can optionally together with the ring form a 5-, 6-, or 7-membered ring.

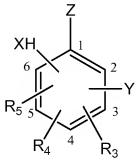
to a primary amine nitrogen atom of a starting peptide molecule, to form a secondary amine, thereby to facilitate conversion of the secondary amine to an amide, activating the C-terminal carboxylic acid group of the peptide, and converting the secondary amine to an amide;

wherein XH in General Formula II is at position 2, and Y is NO_2 at position 6, and further wherein R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, and a covalent linkage to a solid support.

40. (Currently Amended) A method of synthesis of a large peptide with a native peptide backbone, comprising the steps of:

a) synthesizing a set of peptide fragments to be linked to form a large peptide;

b) linking a cyclic aromatic auxiliary compound of General Formula II



II

in which

XH is OH, SH, CH_2OH, or CH_2SH;

Y is an electron-withdrawing group selected from the group consisting of nitro, ketone, carboxylic ester, amide, nitrile, sulfonamide, sulfoxide, sulfone, sulfonate, fluoride, chloride, bromide and iodide;

Z is selected from the group consisting of an alkylalcohol, an alkylhalide, a ketone, and a halogenated C_{1-3} alkyl group, and allows the formation of a covalent carbon-nitrogen bond; and

R^3, R^4 and R^5 are each independently substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, [[-]]aryloxy, XH or Y, or a covalent linkage to a solid support; and

in which R^3 and R^4, or R^4 and R^5 can optionally together with the ring form a 5-, 6-, or 7-membered ring,

to the primary amine of the first peptide fragment to form a secondary amine, thereby facilitating conversion of the amine to an amide;

c) activating the C-terminal carboxylic acid of the second peptide fragment;

d) adding the second peptide fragment to the first peptide fragment and forming a peptide bond between the two fragments; and optionally

e) removing the auxiliary compound after N-acylation is complete,

wherein steps ~~(a) to (e)~~ b) to e) are repeated to add the remaining members of the set of peptide fragments until the large peptide is completed.

The following is an Examiner's Statement of Reasons for Allowance: The following reference is related to the claimed invention. Johnson *et al.* (J. Peptide Sci. 1, 11-25 (1995)) teach the use of salicylaldehyde or 4-methoxysalicylaldehyde (also named as 2-hydroxy-4-methoxybenzaldyhyde; abbreviated as Hmb) to prepare N-(2-hydroxylbenzyl)amino acids or N-(2-hydroxyl-4-methoxybenzyl)amino acids (e.g., N-(2-hydroxyl-4-methoxybenzyl)-L-alanine; page 20; general method 2), which then reacts with Fmoc amino acid symmetric anhydrides in dichloromethane (Table 7). The reference also teaches coupling of Fmoc-alanine to N-substituted tripeptide derivative **14** (R=H and R=Me), it also indicates the analogous 2-hydroxy-4-methoxybenzyl derivative behaved similarly (Table 4), in which when the *o*-methoxyl group was replaced with hydroxyl group, a remarkable rate enhancement for the formation of product was observed (page 15, right column; Table 4), where rapid rearrangement through the 6-membered cyclic intermediate (structure **15**) and some tentative rules regarding the acylation of Hmb-peptide resins for the coupling of Fmoc-Y-OH to (Hmb)X-peptide resin are discussed (pages 16-17). Since 4-methoxysalicylaldehyde contains 2-hydroxy (as XH), 4-methoxy (as Y, a known electron-withdrawing group) and aldehyde (as Z in formula II) and is used to link to an amino acid or tripeptide-resin to form secondary amine (see structure **14**), which then reacts with Fmoc-amino acid with activated carboxylic acid (i.e., pfp or anhydride) to form a peptide bond. However, Johnson *et al.* do not teach or suggest the use of electron-withdrawing group such as nitro, ketone, carboxylic ester, amide, nitrile, or halide at position 5 or 6 in the aromatic auxiliary compound in synthesizing various peptides. Therefore, the claims are allowable over the art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK
December 16, 2009